25

Late complications, including late relapse

Gérard Socié, Rochelle E Curtis, John P Klein

INTRODUCTION

Since its introduction in the early 1970s, allogeneic stem cell transplantation (alloSCT) for chronic myeloid leukemia (CML) has gained wide acceptance.[1] It is generally considered as the only form of therapy with the capacity to cure CML.[2] The efficacy of alloSCT in the treatment of chronic-phase CML has been evaluated in a number of observational studies and several retrospective studies (for reviews, see Goldman,[3,4] Clift et al,[5] and Gratwohl et al[6]). Projected actuarial 3-year to 5-year survival rates in these studies are in the 50–60% range, with slightly lower probabilities of disease-free survival. The prospect of cure in this disease came from projected survival curves that appear to plateau (or taper more slowly) after 3–7 years.[7] However, while SCT was introduced nearly 30 years ago, it is of note that only a few published studies have reported data with a median follow-up of more than 40 months.

During the last decade, new approaches such as the combined use of cyclosporin and methotrexate,[8] or the use of ganciclovir to treat cytomegalovirus (CMV) infection have reduced early treatment-related mortality and improved the general outcome following alloSCT. Furthermore, in CML, the impact of the conditioning regimen on transplant outcomes has been prospectively tested in three randomized studies.[9–11] In the short term, the association of busulfan with cyclophosphamide seemed to be as efficacious as the association of cyclophosphamide with total-body irradiation (TBI). Since some late effects of alloSCT have clearly been linked with the use of TBI,[12] the long-term follow-up of such randomized trials would be of obvious clinical importance. All these changes in the practice of alloSCT may have a strong impact on the incidence and risk factors of late events occurring after transplantation, but, when reporting these data, few studies have restricted the study population to patients transplanted for CML. Thus, we would like to remind the reader that when summarizing the long-term outcome of transplantation in CML in this chapter, we have to deal with a limited number of sets of reported data, in which patients with CML are often mixed with those transplanted for other diseases. As a consequence, what could be considered to be true for the overall population (risk factor or incidence rate) for any complication may not strictly be applied when considering complications in the setting of transplantation for CML.

In this chapter, we will summarize the long-term outcome and causes of late death, the incidence and risk factors of secondary malignancies, and the incidence and risk factors of

non-malignant complications following alloSCT for CML.

LONG-TERM OUTCOME AND LATE RELAPSES AFTER alloSCT

The IBMTR survey

We recently reported the long-term survival and the analysis of late death in a cohort of 6691 patients who survived more than 2 years and were free of their original disease.[13] Among these patients, roughly a third (2146) were transplanted for CML. For the purpose of this chapter, we have analyzed these 2146 CML patients in greater detail. Their characteristics are summarized in Table 25.1. They were transplanted from January 1980 to December 1993, and were disease-free (i.e. without hematological relapse) for at least 2 years after transplantation. Data on these patients had been reported to the International Bone Marrow Transplant Registry (IBMTR) by 221 transplantation centers worldwide. Less than 4% of the population were lost to follow-up within 2 years after SCT. Thus this cohort represents the largest population of long-term survivors studied today. The median duration of follow-up was 80 months. In this analysis, patients who died as a result of a relapse after transplantation were considered to have died of their original disease, even if this was not recorded as the proximate cause of death. Similarly, patients who died of active chronic graft-versus-host disease (GVHD) were considered to have died of this complication even if other complications (e.g. infection or bleeding) were considered as the proximate cause of death. Deaths due to infection included only those among patients without GVHD.

Among the 2146 patients with CML who were free of their primary disease 2 years after transplantation, the probability of surviving for 5 more years was 88%, the probability of relapse 5 years later was 11%, and the probability of relapse-related death was 6%. The primary causes of death are summarized in Table 25.2. As previously reported, recurrent leukemia was the most frequent cause of late death after transplantation for CML (47% of the cases who died after 2 years), with chronic GVHD being the second most frequent cause (36%). However, it is of note that the primary causes of death were strongly influenced by whether or not a T-cell-depleted graft was used. Of the 283 patients who received a T-cell-depleted transplant, 50 (17.7%) died more than 2 years after transplant, as compared with 188 out of 1863 (10%) of those who received a T-cell-replete graft. Relapse accounted for 80% of the causes of late death in patients who received a T-cell-depleted graft, and 36% in those who received a non-T-cell-depleted one.

We then calculated estimates of relative mortality as described by Andersen et al,[14] taking into account differences among patients with regard to age, gender, race, and nationality. Relative mortality with respect to a transplant recipient is the relative risk of dying at a given time post transplantation as compared with a person of similar age, sex, and nationality in the general population. Relative mortalities with 95% confidence intervals that included 1.0 were not considered to indicate significant differences from the rates in a normal population. Among patients who underwent transplantation for CML, the relative mortality rate was 11.2 (95% confidence interval (CI) 8.2–14.1) 5 years after transplantation, and 19.1 (95% CI 8.8–29.4) 10 years after transplantation, as previously described. However, the analysis of the relative mortalities in patients who received a T-cell-depleted transplant or a non-T-cell-depleted graft again disclosed major differences (Figure 25.1).

Finally, multivariate analyses of late death were performed. As shown in Table 25.3, patients who received a T-cell-depleted transplant had a higher risk of transplant-related death than those whose grafts were not T-cell-depleted; patients with active chronic GVHD or previous acute GVHD had higher risks of death not due to relapse.

Table 25.1 Characteristics of 2146 recipients of allogeneic bone marrow transplants who were disease-free 2 years after transplantation for CML

Variable[a]		
Age (in years) median (range)	34	(1–62)
Gender (%):		
Male	1221	(57%)
Female	925	(43%)
Karnofsky score before SCT <90, *n* (%)	228	(11%)
Disease stage before SCT, *n* (%):		
First chronic phase	1716	(80%)
Second chronic phase or accelerated phase	361	(17%)
Blast phase	65	(3%)
Time from diagnosis to SCT (in months), median (range)	12	(1–201)
Type of donor, *n* (%):		
Matched sibling	1812	(84%)
Identical twin	32	(1%)
Mismatched related	104	(5%)
Unrelated	188	(9%)
Prophylaxis against GVHD, *n* (%)		
MTX + CSA ± other drugs	1199	(56%)
MTX ± other drugs (not CSA)	134	(6%)
CSA ± other drugs (not MTX)	493	(23%)
T-cell depletion ± drugs	283	(13%)
Other methods or none	35	(2%)
Year of transplantation, *n* (%):		
1980–1983	151	(7%)
1984–1987	614	(29%)
1988–1990	759	(35%)
1991–1993	622	(29%)
Acute GVHD grade ⩾II, *n* (%)	586	(27%)
Chronic GVHD, *n* (%):		
None before 2 years	1034	(48%)
Resolved by 2 years	393	(18%)
Active by 2 years	716	(33%)

[a]*n*, number; MTX, methotrexate; CSA, cyclosporin.

Table 25.2 Primary causes of death among 2146 recipients of allogeneic bone marrow transplants who were disease-free 2 years after transplantation for CML[a]

Cause of death	Non-TCD graft: late death 188 patients	TCD graft: late death 50 patients	Total: 2146 patients; late death 248 patients
Relapse	68 (36%)	40 (80%)	108 (45%)
GVHD	75 (40%)	6 (12%)	81 (34%)
Infection without GVHD	12 (6%)	2 (4%)	14 (6%)
New cancer	8 (4%)	0 (0%)	8 (3%)
Organ failure	9 (4%)	1 (2%)	10 (4%)
Other	16 (7%)	1 (2%)	17 (7%)
Unknown	10 (5%)	0 (0%)	10 (4%)

[a] Percentages are rounded and may not add to 100%. Other causes of death included: hemorrhage, interstitial pneumonia, and miscellaneous causes.
TCD, T-cell-depleted.

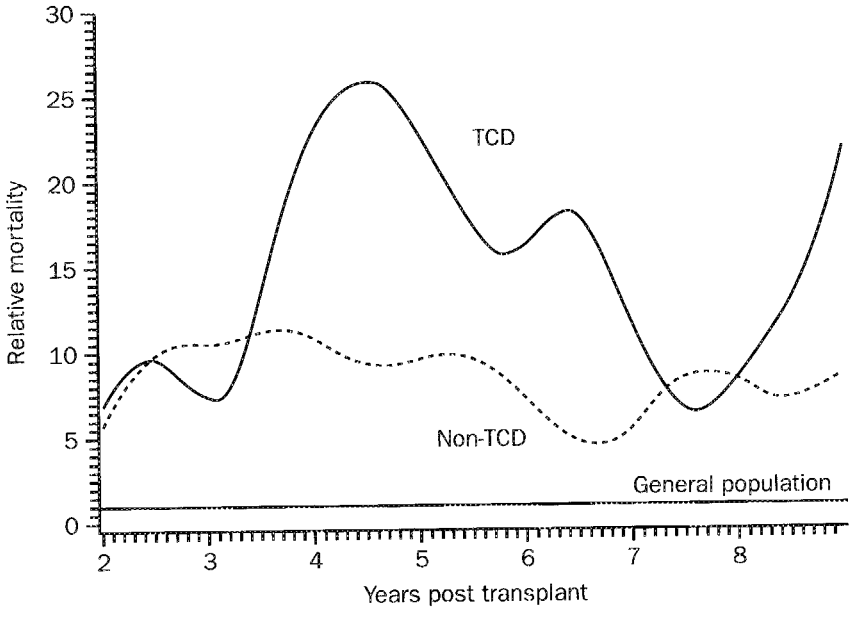

Figure 25.1 Mortality relative to the general population among 2146 recipients of allogeneic bone marrow transplants who were disease-free 2 years after transplantation for CML. TCD, T-cell-depleted.

Long-term follow-up of randomized studies comparing busulfan and cyclophosphamide with cyclophosphamide and TBI as pretransplant conditioning regimen

Two main conditioning regimens are currently used before transplantation for CML: the association of cyclophosphamide (Cy) and total-body irradiation (TBI)[15] and the association of busulfan (Bu) with Cy.[16,17] In the early 1990s, three randomized studies compared the outcome of patients with CML who underwent allogeneic SCT either after Cy–TBI or after Bu–Cy.[9–11] Among these trials, the French trial

Table 25.3 Relative risk (RR) of late death among 2146 recipients of allogeneic bone marrow transplants who were disease-free 2 years after transplantation for CML

Variable	Death from any cause			Death not related to relapse			Death related to relapse		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Disease phase:									
Chronic	1.0		0.002	1.0		0.12	1.0		0.004
Accelerated	1.4	1.0–2.0		1.1	0.7–1.7		1.9	1.3–3.0	
Blast	2.2	1.3–3.7		2.0	1.0–3.9		2.3	1.0–5.8	
T-cell depletion	1.9	1.4–2.6	<0.001	0.7	0.4–1.4	0.34	3.3	2.2–5.0	<0.001
Previous acute GVHD	1.4	1.1–1.9	0.009	2.0	1.4–2.9	<0.001	0.9	0.5–1.4	0.56
Chronic GVHD at 2 years:									
None	1.0		<0.001	1.0		<0.001	1.0		0.09
Resolved	0.7	0.5–1.1		0.9	0.4–1.9		0.7	0.4–1.2	
Active	1.78	1.3–2.4		4.2	2.7–6.6		0.6	0.4–1.0	

and the Seattle group trial included only patients with CML in first chronic phase,[9,10] while the Nordic group trial included not only CML patients at various stages of their disease but also other diagnoses.[11] At present, these trials have more than 7 years' median follow-up. Olle Ringden and co-workers from the Nordic group recently updated their results, showing an increased risk of chronic GVHD, obstructive bronchiolitis, and alopecia in patients who received Bu–Cy as compared with those who were given Cy–TBI, irrespective of the primary diagnoses.[18] In this study, 30 patients with CML received Bu–Cy and 27 Cy–TBI. The updated analysis with 7 years' follow-up in patients with CML in first chronic phase receiving Cy–TBI (24 patients) or Bu–CY (22 patients) did not show any differences in the two arms (Figure 25.2; Olle Ringden, personal communication, November 1999). Similarly, Clift and co-workers from the Seattle group recently updated their results on 69 patients who received Bu–Cy and 73 who were given Cy–TBI. All patients were transplanted in first chronic phase and none had T-cell-depleted grafts. With a median duration of follow-up of more than 7 years, no difference in leukemia-free survival was observed in the two groups (RA Clift, personal communication, August 1999). However, as shown in Figure 25.3, this large study demonstrates that late relapses do occur in patients transplanted for CML (the latest being observed 8 years after transplantation). Furthermore, what is clearly illustrated by these two studies is the apparent equivalence of the two conditioning regimens with regard to disease control. It would thus be of clinical importance to determine the quality of life and the incidences of late malignancies and non-malignant late effects in patients assigned to the two types of conditioning. Such a study is in progress. It will compare in the long term patients who have been enrolled in these two trials, and will update the results of the French trial (by Socié et al).

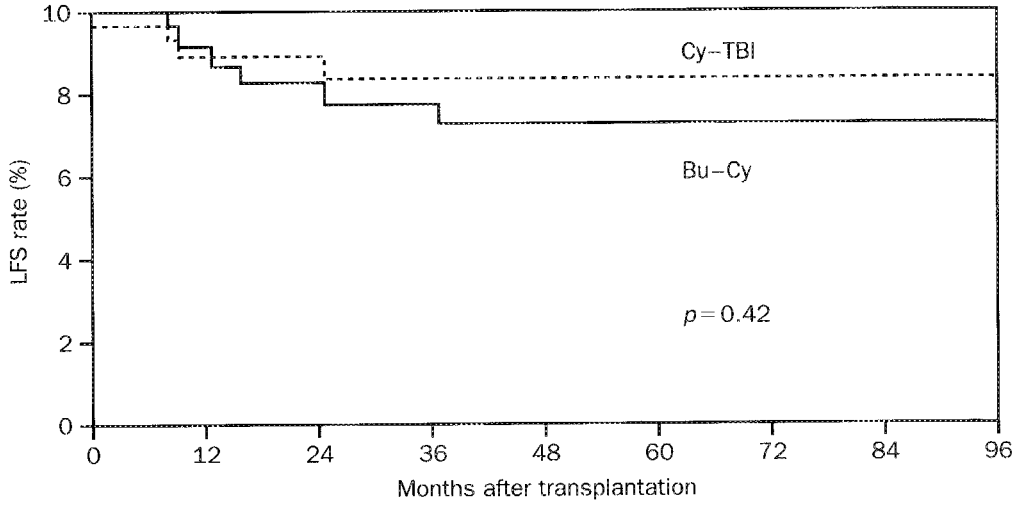

Figure 25.2 Kaplan–Meier estimates of leukemia-free survival (LFS) for 46 patients conditioned for HLA-identical marrow transplantation with the busulfan–cyclophosphamide (Bu–Cy) and cyclophosphamide plus total-body irradiation (CY–TBI) regimens. Updated results from the Nordic Bone Marrow Transplantation Group.

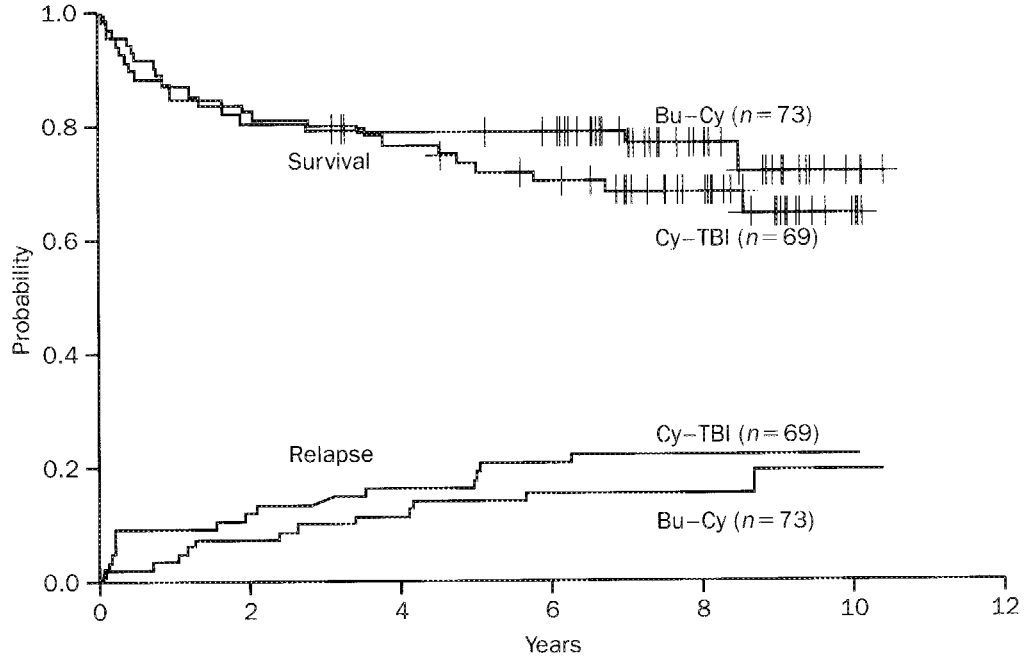

Figure 25.3 Kaplan–Meier estimates of survival and cumulative incidence of relapse for patients conditioned for HLA-identical marrow transplantation with the Bu–Cy or Cy–TBI regimens. Updated results from the Fred Hutchinson Cancer Research Center.

Long-term follow-up after transplantation: literature data with emphasis on late relapses

Most aspects of alloSCT for CML are covered in the other chapters in this volume. However, when we looked for series reported in the literature in which the median follow-up was longer than 3 years (as 'long-term' could be defined), it turned out that only a few data were available.

One of the most useful reports in this regard is the one published by Van Rhee and co-workers on behalf of the European Group for Blood and Marrow Transplantation (EBMT).[19] In this study, data on 373 patients transplanted in first chronic phase of CML using unmanipulated marrow cells from HLA-identical sibling donors were reported. The median follow-up of surviving patients was 7 years. The probabilities of survival and leukemia-free survival at 8 years were 54% and 47%, respectively. Twenty-seven patients died more than 2 years after transplant. Leukemia relapse accounted for more than 40% of these late deaths. Relapse of CML occurred in 40 patients. In a further 7 cases, a transient cytogenetic relapse was observed. Twenty-four patients experienced relapse 2 years after SCT. The latest documented relapse was at 6.5 years. The probabilities of relapses at 2 and 8 years after SCT were 10% (95% CI 7–15) and 18.9% (95% CI 14–25). Late relapses (later than 2 years) were less frequent in patients who developed chronic GVHD (relative risk 0.21) and in patients with female donors (relative risk 0.18). Finally, 67 patients in hematological remission were studied for residual disease by two-step reverse-transcriptase polymerase chain reaction (RT-PCR) for *BCR/ABL* mRNA, and 61 (91%) tested negative. These results closely match those of other cooperative groups and of single-center studies (Table 25.4).

Long-term outcome and comparisons with sibling transplants are still lacking for unrelated transplants. However, it should be noted that reported relapse rates following unrelated SCT for CML seem to be relatively low, especially in patients who received unmanipulated grafts Hansen et al[20,21] for the Seattle group reported an analysis on 196 patients transplanted for CML from an unrelated donor. The median follow-up was over 5 years. Fifteen patients relapsed, yielding a 10% cumulative incidence rate at 5 years. Devergie et al[22] for the EBMT reported a relapse rate as low as 2% in patients transplanted while in chronic phase, from an HLA-DRB1-matched donor, using a non-T-cell-depleted graft. Finally, in a study involving 283 patients by the Minneapolis group,[23] the relapse rate among recipients from unrelated donors (106 patients) was significantly lower (relative risk 0.22) than that in recipients from related donors (177 patients). Patients who underwent SCT from related donors had a median follow-up of 60 months, but those with unrelated donors have only been followed for a median of 20 months.[23]

Finally, studies comparing the outcome of grafted patients with that of non-grafted patients who were treated with interferon-α (IFN-α) have not reported the impact of late relapses in grafted patients.[24,25] This point should be kept in mind, because patients who relapse after transplant may have prolonged survival following donor leukocyte infusion (DLI).

Long-term follow-up after transplantation: concluding remarks

Some data reported here deserve additional comments. First, it is now clear that long-term molecular cure can be achieved after alloSCT in up to 50–60% of patients, provided that they are transplanted in chronic phase. It is therefore important to pay attention to parameters that influence the long-term outcome of these patients, with the aim of reducing both relapse-related and non-relapse-related deaths. Second, data reported in this section, in particular those of the IBMTR survey, are retrospective analyses of patients transplanted some years ago. With the advent of cellular therapy, it may again become possible to use T-cell depletion in

Table 25.4 Long-term follow-up studies of alloSCT for chronic-phase CML

Authors	No. of patients	Conditioning[a]	GVHD prophylaxis[b]	Median follow-up (months)	Relapse rate (%)	OS rate (%)	DFS rate (%)
Van Rhee et al[19]	373	Cy–TBI	CSA ± PDN ± MTX	84	19	54	47
Clift and Anasetti[71]	351	Cy–TBI	CSA + MTX	NR[c]	20	70	60
Devergie et al[72]	170	Cy–TBI	CSA + MTX/TCD	44	19	56	46
Beelen et al[73]	135	Cy–TBI	CSA + MTX	59	17	59	49
Aschan et al[74]	42	Cy–TBI	CSA + MTX/TCD	60–65	NR[c]	38–54	NR[c]
Galimberti et al[75]	34	Bu–Cy	CSA + MTX + PDN	43	0	71	71

[a] Cy, cyclophosphamide; TBI, total-body irradiation; Bu, busulfan.
[b] CSA, cyclosporin; PDN, prednisone; MTX, methotrexate; TCD, T-cell depletion.
[c] Not reported.

patients with high risks of transplant-related mortality (i.e. older patients). In this regard, it is interesting to note that excellent results have recently been reported by the Milwaukee group using T-cell depletion and DLI in patients who eventually relapsed.[26]

SECONDARY MALIGNANCIES AFTER alloSCT

Few studies have assessed the risks of second malignancies among long-term survivors of SCT[27–32] (for a review, see Deeg and Socie[33]). While classically the problem of secondary malignancy has been subdivided into lymphoproliferative disorders, secondary leukemia, and solid cancers, it is mainly the third of these that may arise as late events following SCT. To the best of our knowledge, no cases of secondary leukemia (i.e. leukemia developing in donor cells) have been reported after SCT for CML.

Lymphoproliferative disorders are mainly B-cell malignancies of donor origin occurring mostly during the first year after SCT. In the largest series, involving 18 014 patients, 4770 (26.5%) patients had CML.[34] There was no increased risk per se in CML patients. Risk factors included transplantation from an unrelated or from an HLA-mismatched related donor (relative risk 4.1), T-cell depletion of the graft (relative risk 12.7), grade II–IV acute GVHD (relative risk 1.9), and the use of anti-thymocyte globulin (ATG) (relative risk 6.4) or anti-CD3 (relative risk 43.2) antibody to treat acute GVHD. It is clear that most of these risk factors apply to patients with CML, especially with the growing use of unrelated donors in such patients. In this survey, two additional points deserve comment. First, for the first time, it was clearly demonstrated that the risk of lymphoproliferative disorders in recipients of T-cell-depleted grafts varied greatly with the method used for T-cell depletion (with the highest risk being associated with methods targeting only T cells and/or natural killer (NK) cells and the lowest with the use of Campath-1). Second, this study demonstrated that late-occurring (beyond a year) lymphoproliferative disorders do exist. These late disorders closely resemble non-Hodgkin's lymphoma. None of the above risk factors emerged, and only chronic GVHD was significantly linked with these late lymphomas.

None of the reports on second solid cancers specifically restricted the study population to patients who underwent SCT for CML. The largest study on solid cancers involved 19 229 patients who were transplanted at the Fred Hutchinson Cancer Research Center or reported to the IBMTR.[35] In this cohort, 4885 patients (25.4%) underwent alloSCT for CML. For the purpose of this chapter, data on patients with CML were re-analyzed. Sixteen solid tumors occurred in these 4885 patients, and of these 16 tumors, 14 were invasive. The projected 10-year incidence of invasive solid cancer using Kaplan–Meier estimates was 0.7% (95% CI 0.3–1.1%). The different tumor types and the times between transplant and the occurrence of the cancer are summarized in Table 25.5. We then calculated the observed incidence of invasive cancer in CML patients and compared it with that in the general population, matched for age, gender, and year of diagnosis of cancer. Overall, the observed-to-expected ratio was 1.2 (95% CI 0.6–2). This ratio means that there is a slight but not statistically significant increased incidence of solid cancers in patients transplanted for CML. However, when looking at age at transplantation, there was a significant 9.7 excess risk in patients transplanted before 30 years of age but not in patients older than this (Table 25.6).

NON-MALIGNANT COMPLICATIONS AFTER alloSCT

A number of late complications have already been described, but few data on risk factors for these long-term effects of SCT are available. Besides long-term complications, evaluation of the quality of life (QOL) of cured patients is of obvious importance.[36,37] Our goal is not only to cure the patients of their original disease but also to help them to return to work or school

Table 25.5 Solid cancers developing in 16 patients among 4885 recipients transplanted for CML

No. of tumors	Tumor type	Location	Latency (years)
4	Adenocarcinoma	Breast	0.3, 2.9, 4.2, and 4.1
2	Papillary carcinoma	Thyroid	0.2 and 2.8
2	In situ epidermoid carcinoma	Uterine cervix	1.2 and 3.4
2	Rhabdomyosarcoma	Temporalis muscle, tight	0.7 and 2.7
2	Malignant melanoma	Skin	1.0 and 2.0
1	Malignant fibrous histiocytoma	Liver	1.4
1	Chondrosarcoma	Scapula	15.3
1	Epidermoid carcinoma	Skin	2.2
1	Astrocytoma	Spinal chord	3.2

Table 25.6 Ratio of observed (O) to expected (E) cases and absolute excess risk of new invasive solid cancers according to age at transplantation in patients with CML

Age at transplantation							
Less than 30 years				More than 30 years			
O	E	O : E	Excess risk	O	E	O : E	Excess risk
6	1.4	4.3 ($p < 0.05$)	9.7	8	10.5	0.8	−4.1

and to be able to lead a social life as close as possible to the 'normal' general population. The major goal in assessing late complications after SCT is not only to analyze late complications and QOL of transplanted patients but also to compare them with those of non-transplanted patients. In fact, while some of the late complications might be more frequent after SCT (such as radiation- or steroid-induced cataracts), other late complications have also been described in non-transplanted patients with CML (for a review, see Silver et al[7]). In this section, we will cover only the main non-malignant complications, and will focus on the few data that are available after SCT for CML.

Thyroid abnormalities

Thyroid dysfunction has been recognized as one of the potential late effects of the intensive treatment for obtaining cancer survival. Irradiation and busulfan seem to be the leading causes of thyroid disorders after SCT.[38–42] The most frequent thyroid disorder found in these patients is frank or subclinical primary hypothyroidism (compensated hypothyroidism). Hypothyroidism is a relatively early complication in patients after SCT, but it can also manifest years after transplant. None of the reported series dealing with hypothyroidism after alloSCT looked specifically for this complica-

tion in patients transplanted for CML. Boulad and co-workers[40] reported that in a large series involving 150 patients who were alive and disease-free 1 year after transplantation, 3 out of 36 patients with CML (8%) developed hypothyroidism. In a cohort of 86 patients from Genoa who underwent SCT during childhood (A Cohen et al, unpublished data), 9 (10%) developed frank hypothyroidism (5 received fractionated TBI; 4 received busulfan), 0.5–6 years after transplant (median 1 year); 22 patients (25%) developed subclinical hypothyroidism (18 fractionated TBI; 4 chemotherapy only), 0.5–7 years after transplant (median 3 years). In a series of 77 patients who underwent SCT without the use of TBI, 26 patients had CML (34%).[42] Peripheral thyroid insufficiency was observed in 4 out of these 26 patients (14%), who received Bu–Cy as conditioning regimen (G Socié, unpublished data). Thus, when treating patients with CML, physicians must be aware of this relatively frequent complication, even in the absence of TBI. Regular measurement of thyroid-stimulating hormone (TSH), and free T3 and free T4 thyroid hormones allows early detection of peripheral thyroid insufficiency. Treatment with L-thyroxine is indicated in those cases of frank primary hypothyroidism with high basal TSH concentration and low free thyroid hormone levels. There is a debate on whether or not to treat patients with subclinical hypothyroidism.[43] On the one hand, treatment might induce early osteoporosis in patients who are already at risk of developing osteoporosis due to sex-hormone deficiency. Furthermore, the majority of cases with subclinical hypothyroidism after SCT were found to be mild, compensated, and resolved spontaneously. On the other hand, treatment with L-thyroxine will cause a decrease in TSH levels, which, although not proven, has been incriminated as a contributory factor in thyroid carcinogenesis.[43,44] Thus, treatment of subclinical hypothyroidism should be carefully discussed with an endocrinologist.

Ophthalmologic complications

Cataracts

Cataract formation has been recognized in SCT recipients as one of the first and most frequently occurring late complications of TBI.[45,50] Single-dose TBI of 10 Gy or more causes cataracts in nearly 100% of patients. Fractionation of TBI was first thought to reduce the incidence of this complication; however, it is now clear that fractionated TBI only delays the appearance of cataracts and consequently will probably lead to a high probability of cataracts requiring surgery on the long-term follow-up. In addition to TBI fractionation, TBI dose rate (high dose rate) is an additional risk factor for the development of cataracts. In patients who underwent SCT following irradiation-free conditioning regimens, steroids (given for GVHD prophylaxis and/or treatment) emerge as significant risk factors. Finally, it is not clear at present whether Bu–Cy per se (i.e. in the absence of steroids given for GVHD) will lead to a significant incidence of cataracts. In a series from the Fred Hutchinson Cancer Research Center studying, in the long term, the incidence of and risk factors for developing cataracts in adult patients who received either single-dose or fractionated TBI, 131 patients had CML (the total population studied comprised 492 patients).[47] In patients with CML, the 10-year probability of cataracts was 35% in those who were given fractionated TBI (121 patients) and 42% in patients receiving single-dose TBI (10 patients). In addition to TBI, steroid therapy for GVHD was an independent risk factor. Both in this study from Seattle and in another one from the Basel group,[50,51] single-dose TBI lead to more severe cataracts. Steroid use was a risk factor in both studies. Long-term outcome analysis of patients randomized to receive either Bu–Cy or Cy–TBI from the Nordic group[18] demonstrated that cataract risk was higher in the TBI group (31%) than in the Bu–Cy group (10%, $p = 0.007$) (data according to primary disease unknown). Thus there should be a systematical search for cataracts in patients transplanted for CML, irrespective of

the conditioning regimen used, and surgical treatment discussed when visual acuity is lowered.

Late-onset keratoconjunctivitis sicca syndrome

This complication occurs in nearly 25% of the patients. It is clearly associated with chronic GVHD, older age, and female gender. Adequate treatment can avoid severe corneal defects.[52]

Avascular necrosis of bone

Among late complications, avascular necrosis of bone has been reported, but few studies have included enough patients to allow analysis of the risk factors.[53,56] In a multicenter retrospective study of 4388 patients, 77 developed avascular necrosis, leading to a 4.3% projected incidence at 5 years. Symptoms developed 2–132 months after transplantation. In these 77 patients, a mean of 1.87 joints per patient were affected (range 1–7). The hip joint was the most often affected (88% of patients), and 48% of the patients required joint replacement. All but 2 patients received steroids for acute and/or chronic GVHD over a mean period of 15 months. In multivariate logistic regression analysis, five factors were significantly associated with an increased risk for developing avascular necrosis: chronic GVHD (odds ratio (OR) = 3.52), acute GVHD (OR = 3.73), age over 16 years (OR = 5.81), aplastic anemia (OR = 3.90), and acute leukemia (OR = 1.72).[55] Although patients with CML seemed to have a lower risk of avascular necrosis than patients with either aplastic anemia or acute leukemia, the incidence of this complication in patients with CML was far from negligible. In fact, among 970 patients with CML, 18 developed avascular necrosis, leading to 5-year incidence of 4%.

Fertility

Gonadal failure is an almost-inevitable consequence of high-dose chemotherapy and radiotherapy, and recovery is rare. Over the last two decades, the outcome for patients undergoing high-dose therapy has continued to improve. The inability to parent children, and for women the immediate onset of menopause, are factors that further impair the quality of life of patients with CML, and which must now be addressed. For women, there are a number of risk factors for the development of ovarian failure, including the nature, dose, and duration of treatment. However, the most important factor is the age at the time of transplant, with the incidence of irreversible ovarian failure increasing with increasing age. Furthermore, women who initially recover menses, and even those who subsequently bear children, are more likely to enter menopause at an earlier age than the normal female population. For men, the age at treatment is less important than for women. In contrast, the underlying disease, the type of drug, the total dose, and the duration of administration all affect the likelihood of permanent azoospermia. For both sexes, alkylating agents are more likely to induce infertility than cytotoxics of other drug classes, although the gonadal consequences of modern high-dose combination regimens is virtually unknown (including Bu–Cy).[57]

Within the Late Effects Working Party of the EBMT, there has recently been a survey of the outcome of conceptions from men and women previously treated by transplantation. Information was provided by 199 of 229 European SCT teams. Of these, 71 teams were aware of a total of 261 conceptions, in 199 patients. Although the patients were heterogeneous with respect to underlying disease, treatment prior to transplant, conditioning regimens, and type of transplant, some general conclusions can be drawn. First, parenting a child after transplant is a rare event (as illustrated by numerous case reports in the literature);[58–69] second, the interval from transplant to first conception was longer in patients receiving allo-

grafts than in those receiving autografts, reflecting both an increased time to gonadal recovery and the younger age at transplant. Third, female patients transplanted for hematological malignancies may require assisted conception and appear to experience more complications, including a higher rate of spontaneous abortion. Babies born to these patients are more likely to be born prematurely and to be of low birth weight. Fourth, at present, the children born to such patients do not appear to be at increased risk of congenital malformations and are developing normally. Similar results have been reported from the Seattle transplant team.[70]

Despite these encouraging results, the majority of patients undergoing high-dose therapy will experience at least temporary gonadal failure. For most women, ovarian damage results in immediate menopause, with its troublesome symptoms and loss of sexual interest, and, in the longer term, an enhanced risk of osteoporosis and arterial vascular disease. An immediate and relatively easily satisfied requirement post therapy is therefore adequate hormone replacement therapy (HRT). The goal of HRT must be to find a combination of hormones that suits each individual, thereby controlling symptoms, protecting against future complications, and ensuring compliance with therapy.

The restoration of fertility is more difficult, and at present relies upon semen and embryo cryopreservation prior to treatment. In the future, ovarian, oocyte, and testicular freezing may become a real possibility (for a review, see Apperley and Reddy[57]). Fertilization can now be achieved in vitro by techniques of micromanipulation, thus requiring only a single sperm. It therefore follows that all male patients should be offered semen cryopreservation even if their sperm quality is poor. If a woman has a partner who has agreed to the procedure then cryopreservation of her own fertilized oocytes can be undertaken. Ovarian hyperstimulation is essential for the collection of several oocytes, and the time required for this may not be available in women who require immediate treatment for their underlying disease. For women with chronic illnesses such as CML, this technique may be possible. The ability to collect and fertilize good-quality oocytes is dependent on adequate ovarian function at the time of hyperstimulation. Increasing age and gonadal dysfunction due to prior exposure to chemotherapy will undoubtedly diminish the chances of successful collection cycles. For patients in whom embryo/semen cryopreservation is not practical, there remain three other possibilities to parent a child after transplant. First, following therapy and recovery, patients can receive donated ova or sperm, or donated embryos from an unrelated couple. Second, they could arrange for a surrogate to produce a live infant, and finally, according to local legal requirements, they may be able to adopt an infant.

Finally, one point should be stressed for patients with CML. In the EBMT survey on conception following SCT, three women requiring embryo transfer relapsed post SCT, and all three had CML. It is thus tempting to speculate that relapse in these patients reflected a disturbance of the graft-versus-leukemia effect consequent to pregnancy. However, in this survey, six further female patients with CML conceived and none relapsed with a median follow-up time of more than 3 years post conception. We cannot therefore recommend exclusion of patients with CML from assisted conception programs. We would, however, recommend the following for patients with CML: first, there should be a delay of 2 years after SCT, and patients should be *BCR/ABL*-negative before embarking on pregnancy; second, there should be close molecular monitoring of these patients during and after pregnancy.

ACKNOWLEDGEMENTS

This work was supported by Public Health Service grants (R01-CA54706-07) from the US National Cancer Institute (JPK), and by Contracts CP-51027 and CP-51028 from the US National Cancer Institute (REC).

REFERENCES

1. Thomas ED, A history of haemopoietic cell transplantation. *Br J Haematol* 1999; **105:** 330–9.
2. Gratwohl A, Hermans J, Goldman JM et al, Risk assessment for patients with chronic myeloid leukaemia before allogeneic blood or marrow transplantation. *Lancet* 1998; **352:** 1087–92.
3. Goldman JM, Management of chronic myeloid leukaemia. *Blood Rev* 1994; **8:** 21–9.
4. Goldman JM, The treatment of chronic myeloid leukaemia – much still to be achieved. *J Intern Med* 1994; **235:** 289–91.
5. Clift RA, Appelbaum FR, Thomas ED, Bone marrow transplantation for chronic myelogenous leukemia – Reply. *Blood* 1994; **83:** 2752–3.
6. Gratwohl A, Hermans J, Allogeneic bone marrow transplantation for chronic myeloid leukemia. *Bone Marrow Transplant* 1996; **17:** S7–9.
7. Silver RT, Woolf SH, Hehlmann R et al, An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia: developed for the American Society of Hematology. *Blood* 1999; **94:** 1517–36.
8. Storb R, Deeg HJ, Pepe M et al, Methotrexate and cyclosporine versus cyclosporine alone for prophylaxis of graft-versus-host disease in patients given HLA-identical marrow grafts for leukemia: long-term follow-up of a controlled trial. *Blood* 1989; **73:** 1729–34.
9. Clift RA, Buckner CD, Thomas ED et al, Marrow transplantation for chronic myeloid leukemia: a randomized study comparing cyclophosphamide and total body irradiation with busulfan and cyclophosphamide. *Blood* 1994; **84:** 2036–43.
10. Devergie A, Blaise D, Attal M et al, Allogeneic bone marrow transplantation for chronic myeloid leukemia in first chronic phase: a randomized trial of busulfan–cytoxan versus cytoxan–total body irradiation as preparative regimen: a report from the French Society of Bone Marrow Graft (SFGM). *Blood* 1995; **85:** 2263–8.
11. Ringden O, Ruutu T, Remberger M et al, A randomized trial comparing busulfan vs total body irradiation in allogeneic marrow transplant recipients with hematological malignancies. *Transplant Proc* 1994; **26:** 1831–2.
12. Socie G, Kolb HJ, Ljungman P, Malignant disease after allogeneic bone marrow transplantation: the case for assessment of risk factors. *Br J Haematol* 1992; **80:** 427–30.
13. Socie G, Stone JV, Wingard JR et al, Long-term survival and late deaths after allogeneic bone marrow transplantation. *N Engl J Med* 1999; **341:** 14–21.
14. Andersen PK, Horowitz MM, Klein JP et al, Modelling covariate adjusted mortality relative to a standard population. *Stat Med* 1999; **18:** 1529–40.
15. Clift RA, Appelbaum FR, Thomas ED, Treatment of chronic myeloid leukemia by marrow transplantation. *Blood* 1993; **82:** 1954–6.
16. Santos GW, The development of busulfan cyclophosphamide preparative regimens. *Semin Oncol* 1993; **20:** 12–16.
17. Tutschka PJ, Use of busulfan containing chemotherapy for conditioning patients with leukemia for bone marrow allografting. *Bone Marrow Transplant* 1993; **12:** 34–6.
18. Ringden O, Remberger M, Ruutu T et al, Increased risk of chronic graft-versus-host disease, obstructive bronchiolitis, and alopecia with busulfan versus total body irradiation: long-term results of a randomized trial in allogeneic marrow recipients with leukemia. *Blood* 1999; **93:** 2196–201.
19. Van Rhee F, Szydlo RM, Hermans J et al, Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 1997; **20:** 553–60.
20. Hansen JA, Petersdorf E, Martin PJ, Anasetti C, Hematopoietic stem cell transplants from unrelated donors. *Immunol Rev* 1997; **157:** 141–50.
21. Hansen JA, Gooley TA, Martin PJ et al, Bone marrow transplants from unrelated donors for patients with chronic myeloid leukemia. *N Engl J Med* 1998; **338:** 962–8.
22. Devergie A, Apperley JF, Labopin M et al, European results of matched unrelated donor bone marrow transplantation for chronic myeloid leukemia. Impact of HLA class II matching. *Bone Marrow Transplant* 1997; **20:** 11–19.
23. Enright H, Davies SM, Defor T et al, Relapse after non-T-cell-depleted allogeneic bone marrow transplantation for chronic myelogenous leukemia: early transplantation use of an unrelated donor, and chronic graft-versus-host disease are protective. *Blood* 1996; **88:** 714–20.
24. Baccarani M, Monitoring treatment and survival

in chronic myeloid leukemia. *J Clin Oncol* 1999; **17:** 1858–68.
25. Gale RP, Hehlmann R, Zhang MJ et al, Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. *Blood* 1998; **91:** 1810–19.
26. Drobyski WR, Hessner MJ, Klein JP et al, T-cell depletion plus salvage immunotherapy with donor leukocyte infusions as a strategy to treat chronic-phase chronic myelogenous leukemia patients undergoing HLA-identical sibling marrow transplantation. *Blood* 1999; **94:** 434–41.
27. Witherspoon RP, Deeg HJ, Storb R, Secondary malignancies after marrow transplantation for leukemia or aplastic anemia. *Transplantation* 1994; **57:** 1413–18.
28. Witherspoon RP, Fisher L, Schoch G et al, Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. *N Engl J Med* 1989; **321:** 784–9.
29. Deeg HJ, Socie G, Schoch G et al, Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of results in 700 patients. *Blood* 1996; **87:** 386–92.
30. Lowsky R, Lipton J, Fyles G et al, Secondary malignancies after bone marrow transplantation in adults. *J Clin Oncol* 1994; **12:** 2187–92.
31. Socie G, Henryamar M, Bacigalupo A et al, Malignant tumors occurring after treatment of aplastic anemia. *N Engl J Med* 1993; **329:** 1152–7.
32. Bhatia S, Ramsay NKC, Steinbuch M et al, Malignant neoplasms following bone marrow transplantation. *Blood* 1996; **87:** 3633–9.
33. Deeg HJ, Socie G, Malignancies after hematopoietic stem cell transplantation: many questions, some answers. *Blood* 1998; **91:** 1833–44.
34. Curtis RE, Travis LB, Rowlings PA et al, Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. *Blood* 1999; **94:** 2208–16.
35. Curtis RE, Rowlings PA, Deeg HJ et al, Solid cancers after bone marrow transplantation. *N Engl J Med* 1997; **336:** 897–904.
36. Duell T, van Lint MT, Ljungman P et al, Health and functional status of long-term survivors of bone marrow transplantation. *Ann Intern Med* 1997; **126:** 184–92.
37. Wingard JR, Functional ability and quality of life of patients after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1994; **14:** S29–33.
38. Alfiar FZ, Colwill R, Lipton JH et al, Abnormal thyroid stimulating hormone (TSH) levels in adults following allogeneic bone marrow transplants. *Bone Marrow Transplant* 1997; **19:** 1019–22.
39. Bakker B, Massa GG, vanRijn AM et al, Effects of total-body irradiation on growth, thyroid and pituitary gland in rhesus monkeys. *Radiother Oncol* 1999; **51:** 187–92.
40. Boulad F, Bromley M, Black P et al, Thyroid dysfunction following bone marrow transplantation using hyperfractionated radiation. *Bone Marrow Transplant* 1995; **15:** 71–6.
41. Kauppila M, Koskinen P, Irjala K et al, Long-term effects of allogeneic bone marrow transplantation (BMT) on pituitary, gonad, thyroid and adrenal function in adults. *Bone Marrow Transplant* 1998; **22:** 331–7.
42. Toubert ME, Socie G, Gluckman E et al, Short- and long-term follow-up of thyroid dysfunction after allogeneic bone marrow transplantation without the use of preparative total body irradiation. *Br J Haematol* 1997; **98:** 453–7.
43. Cohen A, Rovelli R, Zecca S et al, Endocrine late effects in children who underwent bone marrow transplantation: review. *Bone Marrow Transplant* 1998; **21:** S64–7.
44. Uderzo C, Vanlint MT, Rovelli A et al, Papillary thyroid carcinoma after total body irradiation. *Arch Dis Child* 1994; **71:** 256–8.
45. Belkacemi Y, Ozsahin M, Pene F et al, Cataractogenesis after total body irradiation. *Int J Radiat Oncol Biol Phys* 1996; **35:** 53–60.
46. Belkacemi Y, Labopin M, Vernant JP et al, Cataracts after total body irradiation and bone marrow transplantation in patients with acute leukemia in complete remission: A study of the European Group for Blood and Marrow Transplantation. *Int J Radiat Oncol Biol Phys* 1998; **41:** 659–68.
47. Benyunes MC, Sullivan KM, Deeg HJ et al, Cataracts after bone marrow transplantation: long-term follow-up of adults treated with fractionated total body irradiation. *Int J Radiat Oncol Biol Phys* 1995; **32:** 661–70.
48. Fife K, Milan S, Westbrook K et al, Risk factors for requiring cataract surgery following total body irradiation. *Radiother Oncol* 1994; **33:** 93–8.
49. Hamon MD, Gale RF, Macdonald ID et al, Incidence of cataracts after single fraction total body irradiation – the role of steroids and graft versus host disease. *Bone Marrow Transplant*

1993; **12:** 233–6.
50. Tichelli A, Gratwohl A, Egger T et al, Cataract formation after bone marrow transplantation. *Ann Intern Med* 1993; **119:** 1175–80.
51. Tichelli A, Late ocular complications after bone marrow transplantation. *Nouv Rev Fr Hematol* 1994; **36:** S79–82.
52. Tichelli A, Duell T, Weiss M et al, Late-onset keratoconjunctivitis sicca syndrome after bone marrow transplantation: Incidence and risk factors. *Bone Marrow Transplant* 1996; **17:** 1105–11.
53. Bizot P, Witvoet J, Sedel L, Avascular necrosis of the femoral head after allogenic bone-marrow transplantation – a retrospective study of 27 consecutive THAs with a minimal two-year follow-up. *J Bone Joint Surg [Br]* 1996; **78B:** 878–83.
54. Fink JC, Leisenring WM, Sullivan KM et al, Avascular necrosis following bone marrow transplantation: a case–control study. *Bone* 1998; **22:** 67–71.
55. Socie G, Cahn JY, Carmelo J et al, Avascular necrosis of bone after allogeneic bone marrow transplantation: analysis of risk factors for 4388 patients by the Société Française de Greffe de Moelle (SFGM). *Br J Haematol* 1997; **97:** 865–70.
56. Wiesmann A, Pereira P, Bohm P et al, Avascular necrosis of bone following allogeneic stem cell transplantation: MR screening and therapeutic options. *Bone Marrow Transplant* 1998; **22:** 565–9.
57. Apperley JF, Reddy N, Mechanism and management of treatment-related gonadal failure in recipients of high dose chemoradiotherapy. *Blood Rev* 1995; **9:** 93–116.
58. Arcese W, Iori AP, Pregnancy and secondary cancer after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1999; **23:** 752.
59. Atkinson HG, Apperley JF, Dawson K et al, Successful pregnancy after allogeneic bone marrow transplantation for chronic myeloid leukaemia. *Lancet* 1994; **344:** 199.
60. Borgnapignatti C, Marradi P, Rugolotto S, Marcolongo A, Successful pregnancy after bone marrow transplantation for thalassaemia. *Bone Marrow Transplant* 1996; **18:** 235–6.
61. Delmer A, Rio B, Bauduer F et al, Pregnancy during myelosuppressive treatment for chronic myelogenous leukaemia. *Br J Haematol* 1992; **82:** 783–4.
62. Gulati SC, Vanpoznak C, Pregnancy after bone marrow transplantation. *J Clin Oncol* 1998; **16:** 1978–85.
63. Lipton JH, Derzko C, Fyles G et al, Pregnancy after BMT – 3 case reports. *Bone Marrow Transplant* 1993; **11:** 415–18.
64. Lipton JH, Virro M, Solow H, Successful pregnancy after allogeneic bone marrow transplant with embryos isolated before transplant. *J Clin Oncol* 1997; **15:** 3347–9.
65. Maruta A, Matsuzaki M, Miyashita H et al, Successful pregnancy after allogeneic bone marrow transplantation following conditioning with total body irradiation. *Bone Marrow Transplant* 1995; **15:** 637–8.
66. Milpied N, Moreau P, Cuillere JC et al, Successful pregnancy after allogeneic bone marrow transplantation following conditioning including a 10-Gy single exposure total body irradiation. *Bone Marrow Transplant* 1996; **17:** 467.
67. Nicholson HS, Byrne J, Fertility and pregnancy after treatment for cancer during childhood or adolescence. *Cancer* 1993; **71:** 3392–9.
68. Rio B, Leturkonirsch H, Ajchenbaumcymbalista F et al, Full-term pregnancy with embryos from donated oocytes in a 36-year-old woman allografted for chronic myeloid leukemia. *Bone Marrow Transplant* 1994; **13:** 487–8.
69. Wang WS, Tzeng CH, Hsieh RK et al, Successful pregnancy following very high-dose total body irradiation (1575 cGy) and bone marrow transplantation in a woman with acute myeloid leukemia. *Bone Marrow Transplant* 1998; **21:** 415–17.
70. Sanders JE, Hawley J, Levy W et al, Pregnancies following high-dose cyclophosphamide with or without high-dose busulfan or total-body irradiation and bone marrow transplantation. *Blood* 1996; **87:** 3045–52.
71. Clift RA, Anasetti C, Allografting for chronic myeloid leukemia. *Baillière's Clin Haematol* 1997; **10:** 319–36.
72. Devergie A, Reiffers J, Vernant JP et al, Long-term follow-up after marrow transplantation for chronic myelogenous leukemia: factors associated with relapse. *Bone Marrow Transplant* 1990; **5:** 379–86.
73. Beelen DW, Graeven U, Elmaagacli AH et al, Prolonged administration of interferon-alpha in patients with chronic-phase Philadelphia chromosome-positive chronic myelogenous leukemia before allogeneic bone marrow transplantation may adversely affect transplant outcome. *Blood* 1995; **85:** 2981–90.
74. Aschan J, Ringden O, Sundberg B et al, Increased

risk of relapse in patients with chronic myelogenous leukemia given T-cell depleted marrow compared to methotrexate combined with cyclosporin or monotherapy for the prevention of graft-versus-host disease. *Eur J Haematol* 1993; **50:** 269–74.

75. Galimberti M, Polchi P, Lucarelli G et al, Allogeneic marrow transplantation in patients with chronic myeloid leukemia in chronic phase following preparation with busulfan and cyclophosphamide. *Bone Marrow Transplant* 1994; **13:** 197–201.